(19) Japanese Patent Office (JP) (11) Laid-open Patent Application

(12) Laid Open Patent Gazette (A) **60-190717**

(43) Laid Open 28 September 1985

(51) Int. Cl.[4]	Code	PO Ref. No.
A 61 K 31/72	ADN	6664-4C

Request for examination: not yet requested

Number of inventions 2 (Total 9 pages)

(54) Title of the invention

Lipid lowering agent and lowering method

(21) Application No. 59-44902

(22) Filing Date 9 March 1984

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SPECIFICATION

1. Title of the invention

Lipid lowering agent and method

2. Claims

1. Lipid lowering agent characterized in that it contains partially degraded dextran with an intrinsic viscosity $[\eta]$ of 0.29-1.1 as an active ingredient.

2. Lipid lowering agent described in Claim 1 characterized in that it contains partially degraded

dextran with an intrinsic viscosity [η] of 0.29-1.1 as an active ingredient and is administered at 3-40 mg/kg body weight/day.

3. Agent described in Claim 1 or 2 which comprises partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 and a pharmaceutically permissible diluent or carrier.

4. Method of treatment for people with hyperlipidaemia or people at risk thereof, characterized by oral administration of partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 to such a person at 3-40 mg/kg body weight/day.

5. Method of treatment described in Claim 4 in which said dose is 4-30 mg/kg body weight/day.

3. Detailed description of the invention

The present invention relates to a lipid lowering agent and lowering method which are useful for lowering lipids such as triglycerides (neutral lipids) and cholesterol (lowering, and suppressing increases), and more particularly it relates to a lipid lowering agent and treatment method which have an outstanding effect in lowering blood lipid and an effect in lowering hepatic lipid levels at low doses, without adverse reactions when administered for long periods or the risk of adverse effects such as diarrhoea or abdominal discomfort due to large doses.

More specifically, the present invention relates to lipid lowering agents which contain partially degraded dextrin with an intrinsic viscosity [η] of 0.29-1.1 as an active ingredient, and more particularly to lipid lowering agents characterized in that they contain partially degraded dextrin with an intrinsic viscosity [η] of 0.29-1.1 as an active ingredient and are administered orally at 3-40 mg/kg body weight/day, and preferably at 4-30 mg/kg body weight/day.

The present invention also relates to a method of treatment for people with hyperlipidaemia or people at risk thereof, characterized by oral administration of

partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 to such a person at 3-40 mg/kg body weight/day, and preferably at 4-30 mg/kg body weight/day.

In recent years, hyperlipidaemia due to an increase in lipid in the blood has attracted attention as an important factor related to conditions such as arteriosclerosis, which have become problem diseases of adults, leading to recognition of the need to lower blood lipid.

In recent years, nutritional fibre has been widely employed as a means for bringing about this lowering of blood lipid, and water-soluble nutritional fibres such as pectin, glucomannan and guar gum are known to manifest a powerful action of this type. However, in animal experiments the efficacious dose of these nutritional fibres is generally 10-30 g/kg body weight/day and clinical doses are extremely high, at 50-500 mg/kg body weight/day, resulting in adverse effects such as nausea, diarrhoea and abdominal discomfort and the additional risk of deficiency in minerals and other nutrients; therefore, these nutritional fibres can hardly be considered to be satisfactory as lipid lowering agents.

Blood glucose lowering agents containing a saccharide selected from indigestible polysaccharides and oligosaccharides, including dextran, are known in the prior art (Japanese Laid-open Patent Application JP 57-146713 A), and this application discloses the use not only of native dextran but also of partially degraded dextran of this type, and discloses the fact that dextran of molecular weight 60,000 (corresponding to an intrinsic viscosity [η] of approximately 0.22) to 90,000 (corresponding to an intrinsic viscosity [η] of approximately 0.275) shows a hypoglycaemic effect.

However, said JP 57-146713 A does not discuss the hypoglycaemic effect of partially degraded dextran other than dextran of a molecular weight of 60,0000 to 90,000, neither is it mentioned that dextran has an effect on

lipids such as triglycerides and cholesterol in blood. Therefore, it follows that it also neither discloses nor suggests any relationship between the molecular weight of dextran and an effect of said dextran on lipid.

Moreover, *New Food Industry*, Vol. 25, No. 3 (1983), pp. 13-15, has a report on α-1,6 polysaccharides, including dextran, "in connection with the development of granular sugar with an additive which suppresses elevation in blood glucose". This article reports that when rats were given granulated sugar containing added dextran with a molecular weight of approximately 70,000 (corresponding to an intrinsic viscosity $[\eta]$ of approximately 0.23) there was a suppression in the elevation of blood sugar, with the greatest effect being obtained by adding said dextran to granulated sugar at 1/1000.

However, this article also does not discuss partially degraded dextran with a molecular weight other than the molecular weight mentioned above. Nor is there any mention or suggestion of a relationship between the molecular weight or intrinsic viscosity $[\eta]$ of dextran and the effect of said dextran on lipids.

On the other hand, US Patent 3,148,114 (published 8 September 1964) discloses a method for lowering blood cholesterol. This document presents examples of chemically exceedingly diverse mucilaginous substances which show a cholesterol-lowering effect, including dextran produced by the action of microorganisms on sucrose.

This document does not mention the molecular weight or intrinsic viscosity $[\eta]$ of the dextran employed; however, it gives as an example native dextran such as dextran produced by the action of *Leuconostoc dextranicum*. The molecular weight of native dextran obtained by the action of *Leuconostoc dextranicum* or *Leuconostoc mesenteroides* is usually taken to be of the order of 4,000,000 to 10,000,000.

Moreover, this document gives 50-500 mg/kg body weight/day as an example of the dose of mucilaginous

substance, and indicates a maximum advantage in lowering blood cholesterol when a mucilaginous substance is added to food in the range 5-30 g/kg; and with native dextran at the doses indicated in the aforementioned example there is a risk of diarrhoea and abdominal discomfort.

Furthermore, this document does not mention an effect of dextran or other mucilaginous substances on triglyceride.

This document also does not mention partially degraded dextran of the intrinsic viscosity [η] specified in the present invention. Therefore, it follows that it also does not disclose or suggest any discovery of a relationship between the molecular weight or intrinsic viscosity of partially degraded dextran and the effect of said dextran on lipids.

The present inventors have conducted studies directed towards the development of lipid lowering agents without adverse effects due to long-term use or dose, using dextran, which is safe from the point of view of toxicity.

As a result, we discovered that there is a close correlation between the intrinsic viscosity [η] of dextran and the effect of said dextran on lipids. As the result of further studies based on this discovery, we discovered that partially degraded dextran having an intrinsic viscosity [η] within a specific range shows an outstanding effect in lowering and suppressing increases in triglyceride and cholesterol in blood at low doses, and does not cause adverse effects due to long-term administration or dose.

In these studies the present inventors discovered that partially degraded dextran with an intrinsic viscosity [η] in a range 0.29-1.1, which differs from the ranges of intrinsic viscosity [η] in the prior art as discussed above, is a unique lipid lowering agent which, when administered for example at 3-40 mg/kg body weight/day, and preferably 4-30 mg/kg body weight/day, has an outstandingly marked effect in lowering triglyceride and cholesterol in blood and suppressing

increases, without the risk of producing adverse effects with long-term administration, and also has a marked effect in lowering hepatic lipid.

Therefore, the object of the present invention is to offer outstanding lipid lowering agents and a method for treatment of people with hyperlipidaemia or at risk thereof.

The above object of the present invention as well as many other objects and advantages thereof will become clearer from the description below.

Lipid lowering agents of the present invention contain partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 as an active ingredient. Such partially degraded dextran is in itself known, and can be obtained, for example by partial hydrolysis, using a known method, of native dextran produced from sucrose by a known method employing a known strain of a bacterial species such as *Leuconostoc mesenteroides* or *Leuconostoc dextranicum*, and is also available commercially.

In the present invention, partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 (corresponding to a molecular weight of approximately 100,000 to approximately 1,500,000) is selected as this partially degraded dextran. This partially degraded dextran can be safely used because it has extremely low toxicity (LD_{50}), with oral toxicity (in mice) of $\geq$10 g/kg.

In passing, the intrinsic viscosity [η] of the partially degraded dextran in the present invention is calculated from determinations as follows.

Determination/calculation of intrinsic viscosity [η]

0.05-0.2 g of dextrin is dissolved in water and made up to exactly 100 ml as the sample solution. The flow times of said sample solution and the water employed are determined at 25 $\pm$ 0.02°C using an Ubbelohde viscosimeter, and the intrinsic viscosity is calculated from the following equation.

Intrinsic viscosity [η] = Ln(flow time of sample solution (s)/flow time of water (s))/weight of

sample (g).

The weight average molecular weight ($\bar{M}w$) of the dextrin sample can be found from the intrinsic viscosity above, by the following equation.

$$[\eta] = 9.00 \times 10^4 \bar{M}w^{0.80}$$

Lipid lowering agents of the present invention, which contain partially degraded dextran with an intrinsic viscosity $[\eta]$ of 0.29-1.1 and preferably 0.3-1.06 as an active ingredient, have an effect on triglycerides and cholesterol at low doses, and can show an outstanding lowering effect unaccompanied by any adverse effects. A dose (oral) of 3-40 mg/kg body weight/day, and preferably 4-30 mg/kg body weight/day can be given as an example of said dose. Moreover, the active ingredient in the present invention has an outstanding lowering effect on triglyceride in blood in addition to cholesterol, and also has a noticeable lowering effect on hepatic lipid. According to studies by the present inventors, native dextran (molecular weight approximately 4,000,000 to 10,000,000) does not have a practical effect in lowering triglyceride at low doses, and increasing the dose is accompanied by the risk of adverse effects; however, the active ingredient in the present invention shows an outstanding effect in lowering blood triglyceride and cholesterol at low doses, and also shows an outstanding effect in lowering hepatic lipid, and is not accompanied by any adverse effects.

Therefore, the present invention can offer lipid lowering agents characterized in that they contain partially degraded dextran with an intrinsic viscosity $[\eta]$ of 0.29-1.1 and are given orally at 3-40 mg/kg body weight/day, and preferably 4-30 mg/kg body weight/day.

Lipid lowering agents of the present invention can be presented in any oral dosage form, such as soft capsules, hard capsules, granules, pills, powders, tablets, syrups, lozenges and elixirs, for example. The procedures for making such preparations are well known to a person skilled in the art, and these can be

employed for the present invention.

Lipid lowering agents of the present invention can also be presented in the form of compositions which contain a pharmaceutically permitted diluent or carrier in addition to partially degraded dextrin with an intrinsic viscosity [η] of 0.29-1.1. The content can be selected to suit the preparation; however, approximately 1 to approximately 99%, and preferably approximately 5 to approximately 95% of the weight of the composition can be given as examples of said content.

Examples of diluents and carriers that can be used in such compositions include karaya gum, gum arabic, tragacanth, guar gum, carrageenan, sodium alginate, casein, gelatine, gluten, potato starch, wheat starch, maize starch, rice starch, sweet potato starch, agar, shellac, glucomannan, poly(vinylpyrrolidone), poly(vinyl alcohol), poly(vinyl acetate), polyethylene glycol, methylcellulose, ethylcellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylstarch, carboxymethylstarch, cellulose phthalate acetate, hydroxypropylmethylcellulose phthalate, sodium bicarbonate, magnesium hydroxide, calcium lactate, calcium carbonate, calcium phosphate, synthetic aluminium silicate, magnesium stearate, magnesium metasilicate aluminate, silicic acid, talc, boric acid, calcium sulphate, benzoic acid, citric acid, succinic acid, tartaric acid, gluconic acid, glycerine, sucrose, mannitol, dextrose, sorbitol, lactose, fructose, saccharine, water and ethanol.

The present invention can also offer a method of treatment for people with hyperlipidaemia or people at risk thereof, characterized by oral administration of partially degraded dextran with an intrinsic viscosity [η] of 0.29-1.1 to such a person at 3-40 mg/kg body weight/day, and preferably at 4-30 mg/kg body weight/day. The dose can be in the form of a composition of the agent as in the example above, or the partially degraded dextran can be given as it stands. The dose above is the quantity of partially degraded dextran as

such, and compositions should be administered to give the dose above of contained partially degraded dextran. It can also be administered mixed with food.

The hyperlipidaemia can be primary familial or idiopathic hyperlipidaemia, which constitutes a factor in arteriosclerotic diseases such as coronary arteriosclerosis (ischaemic heart disease and myocardial infarction) and cerebral arteriosclerosis (cerebral infarction and cerebral thrombosis) and fatty liver, etc., or secondary hyperlipidaemia induced by conditions such as obesity, diabetes abnormalities or sugar metabolism or hyperinsulinaemia, etc. Partially degraded dextrin of the present invention can also be given to patients with one of the conditions above who are at risk of induced secondary hyperlipidaemia and to other people at risk of hyperlipidaemia (including healthy individuals).

The lipid lowering effects of dextran are illustrated below.

Experimental Example 1

Male Wistar rats weighing about 105 g were reared for 14 days on a high sucrose diet including dextrans with an intrinsic viscosity $[\eta]$ of 0.11-1.72 (high sucrose diet : dextran = 500 : 1) *ad libitum*, and then serum triglyceride (TG), serum total cholesterol (TC) and blood glucose were determined by the usual methods.

The results are shown in Table 1.

Table 1

Feed	Dextran intrinsic viscosity [η]	Rats	TG (mg/dl)	TC (mg/dl)	Blood glucose (mg/dl)
High sucrose (control)		8	140 ± 22.3	139 ± 21.7	86 ± 8.7
High sucrose plus dextran (test)	0.11	8	126 ± 18.4	134 ± 20.6	84 ± 7.4
	0.26	8	121 ± 17.9	126 ± 17.7	85 ± 8.5
	0.30	8	110 ± 16.7*	113 ± 14.3*	86 ± 7.8
	0.53	8	90 ± 11.1*	107 ± 20.1*	83 ± 8.3
	0.74	8	93 ± 13.9*	111 ± 17.4*	86 ± 7.1
	1.06	8	112 ± 14.7*	118 ± 16.3*	86 ± 11.4
	1.24	8	122 ± 17.3	127 ± 19.8	85 ± 9.2
	1.72	8	131 ± 17.8	130 ± 18.6	88 ± 7.3

Mean ± SD; * significantly different from the control group ($p<0.05$)

As indicated in Table 1, in the test groups given the high sucrose diet including dextran the increase in TG and TC was less than in the control group given the high sucrose diet without dextran. In particular, there was a significant suppression of increases in TG and TC in the groups when dextran with an intrinsic viscosity [η] of 0.30 to 1.06 was included. There was no noticeable effect on blood glucose.

Experimental Example 2

Male Wistar rats weighing about 105 g were reared for 14 days on a high sucrose diet including different proportions of dextran with an intrinsic viscosity [η] of 0.63 *ad libitum*, and then serum triglyceride (TG), serum total cholesterol (TC) and hepatic lipid were determined. The results are presented in Table 2.

Hepatic lipid was found by homogenizing fresh liver in 30 times its weight of acetone, centrifuging and then weighing the supernatant after evaporation to dryness.

Table 2

Feed	Dextran inclusion (g/kg feed)	Rats	TG (mg/dl)	TC (mg/dl)	Hepatic lipid (mg/g wet)
High sucrose (control)		8	144 ± 17.8	139 ± 20.9	124 ± 11.3
High sucrose plus dextran (test)	0.25	8	135 ± 19.5	137 ± 15.4	121 ± 14.1
	0.5	8	117 ± 12.1*	117 ± 18.1*	109 ± 14.0*
	1.0	8	101 ± 15.3*	112 ± 17.5*	104 ± 13.3*
	2.5	8	99 ± 11.5*	111 ± 13.9*	101 ± 15.8*
	5.0	8	112 ± 16.0*	119 ± 14.0*	109 ± 13.5*
	10.0	8	129 ± 15.7	125 ± 21.6	117 ± 14.1

Mean ± SD; * significantly different from the control group ($p<0.05$)

As indicated in Table 2, increases in TG, TC and hepatic lipid were significantly suppressed compared with the control group in the groups given the high sucrose feed including 0.5-5 g of dextran with an intrinsic viscosity [η] of 0.63.

The composition of the high sucrose feed used in Experimental Examples 1 and 2 was as follows.

Sucrose	69.9%
Casein	25%
Vitamin mix (Panvitamin powder)	0.85%
Mineral mix (Harper salts)	4%
Choline chloride	0.15%
Corn oil	0.1%

Experimental Example 3

Male Wistar rats weighing about 110 g were reared for 14 days on a high fat diet including dextran of intrinsic viscosity [η] 0.53 (high fat diet : dextran = 500 : 1), and TG and TC were determined by the usual methods.

The results are shown in Table 3.

Table 3

Feed	Rats	TG (mg/dl)	TC (mg/dl)
High fat diet (control group)	7	133 ± 15.5	200 ± 44.6
High fat diet plus dextran (test group)	7	114 ± 15.2*	148 ± 28.0*

Mean ± SD; * significantly different from the control group ($p<0.05$)

As shown in Table 3, increases in TG and TC were significantly suppressed in the test group given the high fat diet including dextran of intrinsic viscosity [η] 0.53 compared with the control group given the high fat diet without dextran.

The composition of the high fat feed used in Experimental Example 3 was as follows

Sucrose	61%
Casein	22%
Vitamin mix (Panvitamin powder)	0.85%
Mineral mix (Harper salts)	4.0%
Choline chloride	0.15%
Corn oil	1.0%
Cholesterol	1.0%
Lard	10%

Example 1

Tablets (400 mg/tablet) with the composition below were made by the usual method.

Dextran ([η] = 0.53)	25%
Sucrose	25%
Lactose	48.5%
Hydroxypropylcellulose	0.5%
Magnesium stearate	1%

Example 2

A mixture with the composition below was filled into No 1 gelatine capsules (200 mg/capsule), to give a capsule preparation.

Dextran ([η] = 0.63)	80%
Calcium hydrogenphosphate	19%
Magnesium stearate	1%

Example 3

Granules with the composition below were made by the usual method.

Dextran ([η] = 0.75)	50%
Lactose	48%
Hydroxypropylcellulose	2%

Example 4

Tablets (250 mg/tablet) with the composition below were made into sugar-coated tablets by the usual method.

Dextran ([η] = 0.80)	40%
Wheat flour	4.5%
Crystalline cellulose	10%
10% Potato starch paste	45%
Talc	0.5%

Example 5

A solution with the composition below was dispensed into suitable containers and sterilized to give a liquid preparation.

Dextran ([η] = 0.30)	15%
Sucrose	3%
Glucose	5%
Distilled water	77%

Example 6

A lozenge preparation (1 g/lozenge) with the composition below was made by the usual method.

Dextran ([η] = 1.06)	15%
Malt syrup	25%
Sucrose	57%
Gum arabic	3%
Distilled water	balance

Example 7

A powder preparation with the composition below was made by the usual method.

Dextran ([η] = 0.41)	70%
Maize starch	19%
Lactose	20%
Magnesium stearate	1%

Example 8

200 mg aliquots of dextran ([η] = 0.53) were filled

into No. 1 gelatine capsules to give a capsule preparation.

Clinical Example 1

10 patients with high levels of blood triglyceride were given capsules filled with dextran ($[\eta]$ = 0.53) three times daily at every meal for 4 weeks. Values for TG before and after taking dextran are presented in Table 4.

Table 4

Patient		Dextran intake (mg/kg/day)	TG (mg/dl)		
Sex	Age		Before	After	Decrease (%)
F	49	2	520	540	-4
M	60	2	470	420	11
F	63	4	430	320	26
M	58	4	580	400	31
F	53	10	1200	810	32
M	57	10	520	330	37
M	61	30	2200	1150	48
M	55	30	540	390	28
M	47	50	710	610	14
M	54	50	530	470	11

As shown in Table 4, in 10 patients with high levels of blood triglyceride taking dextran with an intrinsic viscosity $[\eta]$ of 0.53 at 2-50 mg/kg body weight/day, TG was decreased in patients taking 4-50 mg/kg body weight/day. and the decrease was particularly great with 4-30 mg/kg body weight/day.

No adverse effects due to dextran intake were noted in patients taking 2-30 mg/kg body weight/day, but tendency towards soft stools was observed with 50 mg/kg body weight/day.

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